Comparative Efficacy of Venlafaxine and Other Medications in Migraine: A Meta-Analysis with Trial Sequential Analysis

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ABSTRACT

This meta-analysis with trial sequential analysis (TSA) evaluated the efficacy of venlafaxine in migraine prevention through database searches from inception to 1st November 2024. A total of eight studies involving 582 patients were included. Results demonstrated venlafaxine's superior overall efficacy (OR = 18.71, p = 0.0008) and significant reductions in multiple outcomes, including Visual Analogue Scale Score (MD = -0.83, p = 0.03), migraine days (MD = -1.59, p = 0.02), Dizziness Handicap Inventory (DHI)-total (MD = -5.16, p = 0.01), DHI-physical (MD = -1.73, p = 0.02), DHI-emotional (MD = -2.04, p = 0.02), vertigo severity scores (MD = -1.18, p = 0.0007), and analgesic use (MD = -3.32, p <0.001). No differences were observed in withdrawals due to adverse reactions and any other reasons, including DHI-functional change, duration, frequency change in the Venlafaxine group VLF *versus* the Other medicines group. TSA revealed insufficient evidence for dizziness improvement (DHI-total: required information size [RIS] = 614 *versus* currently available size = 242), requiring 372 additional patients to confirm stability and mitigate false positives. While venlafaxine showed advantages over most comparators in efficacy and safety measures, these findings require further validation through larger-scale studies.

Key Words: *Migraine, Venlafaxine, Meta-analysis, Trial sequential analysis, Efficacy*.

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INTRODUCTION

Migraine is a chronic neurological disorder with a global prevalence of 12% that causes disabilities.[1] It often causes unilateral or bilateral pulsating headache. The accompanying symptoms include photophobia, nausea, vomiting, aura, and other related manifestations.[2] The 2016 Global Burden of Disease Study has ranked migraine as the second leading cause of years lived with disability (YLD)[3] Migraine has significant adverse economic and societal effects because it impairs patients' quality of life, work, and social activities.[1,4,5] Migraine can be classified into three subtypes: migraine without aura, migraine with aura, and chronic migraine.[6] It was widely believed that the pathogenesis of migraine involves peripheral and central activation of the trigeminal vascular system.[7] The neurophysiological basis of migraine aura is thought to stem from cortical spreading inhibition.[8] Genetic factors, monoamine dysfunction, ovarian hormones, and other elements have been used to explain the comorbidities associated with chronic migraine.

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Venlafaxine is an antidepressant medicine without reliable evidence for migraine treatment. Newly included trials have failed to provide high-quality evidence for its efficacy. No significant benefits over placebo or amitriptyline were observed in reducing attack frequency, intensity, or duration within 3 months, and its long-term safety remains unestablished.[9]

The treatment plan for migraine pathogenesis was not unified.[10] Sumatriptan, introduced in 1992 as the first specific medication for acute migraine attacks, remains a recommended first-line agent in the 2022 Chinese guidelines for the diagnosis and treatment of migraine. For preventing migraine, several medicines can be used, such as β-blockers, tricyclic antidepressants, flunarizine, antiepileptics, and Onabotulinumtoxin A.[11] Anti-calcitonin gene-related peptide (CGRP) is also a safe and well-tolerated option for migraine prevention.[12] Additionally, 5-HT receptor agonists have been used for preventive treatment.

Serotonin–norepinephrine reuptake inhibitors (SNRIs) have been found to be clinically safer and more effective for migraine and vestibular migraine (VM) prophylaxis compared with placebo, and not inferior to other active medication.[13] Norvenlafaxine, duloxetine, levomilnacipran, venlafaxine and others are involved in SNRIs, which exert dual mechanisms of action on serotonin and norepinephrine. Venlafaxine, one of the SNRIs, has been shown to clinically effective and safe in the treatment of depression.[14] In recent years, it has been shown potential in the prophylaxis of migraine.[15,16] Although a previous meta-analysis

assessed the efficacy and tolerability of venlafaxine and duloxetine for VM, several new randomised controlled trials (RCTs) were not included in that published meta-analysis.[17-19] First, the conclusions were not reasonable due to insufficient appraisal of the effect size of SNRIs in migraine prevention. Moreover, the minimum important difference (MID), which is important for migraine sufferers, was not taken into account.[20]

Therefore, the present updated meta-analysis with trial sequential analysis (TSA) was conducted to evaluate the efficacy, tolerability, and consistency of venlafaxine's effect in migraine prevention. The study aimed to determine the potential role of venlafaxine in migraine prophylaxis based on its efficacy and safety profile, and to assess whether further clinical trials are warranted by calculating the required information size (RIS).

METHODOLOGY

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which were strictly adhered throughout the process. Related articles published from the inception of each database to November 2023 were searched in the Cochrane Library, PubMed, Excerpta Medica Database, Web of Science, China National Knowledge Infrastructure, VIP, and WanFang databases. The search formula was formed by the following search words, including text words and Medical Subject Headings (MeSH) terms related to venlafaxine hydrochloride and migraine disorders. In the review process, language was not considered to be a barrier for judging the qualification.

The included literatures consisted entirely of case-control studies comparing the effects of venlafaxine and other medications in the treatment of migraine. The study results directly reported the sample size and 95% confidence interval (CI), or these could be calculated from the data provided in the article. The patients included in this study were diagnosed with migraine in accordance with internationally recognised diagnostic criteria. The Treatment group received venlafaxine either alone or in combination with other medications, while the Control group was given a placebo or other alternative medicines. Studies were excluded if they were non-controlled case studies, lacked essential information, had incomplete foundational details, or were of low quality.

Two researchers independently reviewed the relevant articles and extracted data using a standardised Excel 2010 spreadsheet. The initial screening of titles and abstracts was performed separately, and studies that met the inclusion criteria were selected for the meta-analysis. Any disagreements were resolved through consulting with a third reviewer until agreement was reached.

The targeted outcome measures included the number of migraine days from baseline to post-treatment, duration, severity, analgesic consumption, adverse events (AFs), global efficacy, Dizziness Handicap Inventory (DHI) scores, Vertigo Severity Score (VSS), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), frequency, Visual Analogue Scale (VAS), Hamilton Anxiety Rating Scale (HAMA), and the 24-item Hamilton depression scale (HAMD) scores. During data extraction, continuous variables represented as median were converted to mean and standard deviation (SD) using the method proposed by Luo *et al*.[21,22]

A modified Newcastle-Ottawa Quality Assessment Scale (NOS) was used by two authors to independently evaluate the quality of the included studies [Wells, Shea, and O'Connell *et al*. The Newcastle–Ottawa scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available: https://www. ohri.ca/programs/clinical_epidemiology/oxford.asp]. Five dimensions were assessed: sample size, representativeness, response rate, validity of mental health assessment, and robustness of statistical methods. Study quality was graded using a star-based system with a maximum score of 10. Score of 9–10-indicated as very good, 7–8 good, 5–6 satisfactory, and 0–4 unsatisfactory. If there was any inconsistency in quality assessment between the two authors, it was resolved through discussion until consensus was reached.

Review Manager 5.3 was used for the meta-analysis. Odds ratio (OR) and 95% confidence interval (CI) were used to combine the effect sizes. Heterogeneity was assessed using the inconsistency index value (I^2) and the Q test. An I^2 value between 25% and 50% with $p < 0.05$ indicated mild heterogeneity; a value between 50% and 75% indicated moderate heterogeneity; a value >75% with $p < 0.05$ indicated severe heterogeneity. A random-effects model was used when I^2 was >25%, whereas a fixed-effects model was applied when I^2 was <25%. When the number of the documents was <7, heterogeneity analysis was conducted according to the principles of small-size meta-analysis.[23] Descriptive evaluation was performed for outcome indicators that could not be quantitatively evaluated.

In conducting the TSA, the RIS was determined using the TSA version 0.9.5.10 Beta software. The following prespecified parameters were set as follows: $\alpha = 0.05$ two-tailed, type I error α and $\beta = 20\%$ (power = 80%).

RESULTS

Eight studies with 6 articles in English and 2 articles in Chinese were included. The cumulative sample size was 582, with 304 cases in the Venlafaxine group and 278 cases in the other medications group, as shown in Figure 1. According to the NOS scores, one study was given 6 scores, three articles were given seven scores, two articles were given eight scores, and two articles were given nine scores. The basic information and the NOS scores of the included literature are given in Table I. An unclear risk of bias in random sequence generation was found in three articles. There was an unclear risk of bias in allocation concealment in four of the included reports, and a high risk existed in one of the included reports. Two of the included reports showed an unclear risk of bias in the blinding of outcome assessment, while one of exhibited a high risk. Additionally, four studies demonstrated an unclear risk of bias in the blinding of outcome assessment, one showed an unclear risk of bias in incomplete outcome data, and another showed an unclear risk of bias in allocation concealment, with one of them rated as high risk.

Table I: The basic information and remarks of the included papers.

First author	Year	Country	Study design	Patients (Venlafaxine Group / Control Group)	Male/female		Age		Duration	Outcomes	NOs Scores
					Venlafaxine Group		Control Group	Venlafaxine Group	Control Group		
Rong	2021	China	RCT	56/56	18/94	10/46	48.1 ± 8.0	46.6 ± 8.6	12 weeks	1,2,5,7,10	7
Salviz	2015	Turkiye	RCT	31/33	28/3	31/2	41.6 ± 9.5	38.2 ± 10.1	12 weeks	3,4,5,6,12	9
Tarlaci	2009	Turkiye	RCT	47/58	17/76		31.4 ± 7.8		3 months	1,2,3,4,13	7
Bulut	2004	Turkiye	RCT	26/26	8/44		32.2 ± 8.6		12 weeks	1,2,3	8
Liu	2017	China	RCT	23/22, 20	16/7	13/29	53.2 ± 15.6	51.9 ± 15.55	3 months	3,5,7,12	7
Ozyalcin (V75)	2005	Turkiye	RCT	20, 21/19	17/3	18/1	34.3 ± 8.3	38.2 ± 11.2	10 weeks	1,2,3,4,6,7,8,9,10,14	9
Ozyalcin (V150)	2005	Turkiye			19/2		37.2 ± 12.4				
Hedayat	2022	Iran	RCT	40/40	24/16	22/18	32.4 ± 2.0	33.6 ± 2.0	8 weeks	1,7	8
Huang	2021	China	RCT	40/39	-	-	-	-	3 months	1,2,3	6

Note: Combine groups of means and SD were computed into a single group by decomposing the mean and SD by the online programme available at https://www.statstodo.com/CombineMeansSDs.php. RCT: Randomised controlled trial. Outcome measures; 1: Migraine duration; 2: VAS; 3: Attack frequency; 4: BDI 5: DHI; 6: BAI 7: Adverse reaction; 8: Global efficacy; 9: Analgesic use; 10: HAMA; 11: HAMD; 12: VSS; 13: Lost work day equivalent (LWDE) index; 14: Migraine Disability Assessment Questionnaire; 15: Headache days from baseline to post-treatment (or placebo).

Table II: The pooled effect of the outcome indicators by different models (venlafaxine *versus* other medications).

Outcome indicators	Fixed model of consolidation effect	Random-model of consolidation effect
Withdrawals due to AEs in the Venlafaxine group *versus* the Placebo group	7.14 (0.38, 133.60)	3.70 (0.42, 32.30)
Withdrawals due to any reasons in the Venlafaxine group *versus* the Placebo group	4.33 (0.71, 26.30)	4.11 (0.66, 25.47)
Withdrawals due to adverse reactions in the Venlafaxine group *versus* the Other medicines group	0.25 (0.06, 1.03)	0.25 (0.06, 1.04)
Withdrawals due to any reasons in the Venlafaxine group *versus* the Other medicines group	2.68 (1.11, 6.46)	2.18 (0.11,41.85)
VAS in the Venlafaxine group *versus* the Placebo group	-0.83 (-1.58,-0.09)	-1.13 (-2.30, 0.04)
VAS in the Venlafaxine group *versus* the Other medicines group	-0.08 (-0.32, 0.17)	-0.24 (-0.75, 0.26)
Migraine duration in the Venlafaxine group *versus* the Placebo group	-2.14 (-14.04, 9.76)	-2.14 (-14.04, 9.76)
Migraine duration in the Venlafaxine group *versus* the Other medicines group	-1.80 (-6.32, 2.71)	-0.06 (-1.05, 0.92)
Migraine frequency change in the Venlafaxine group *versus* the Other medicines group	-0.15 (-0.52, 0.22)	0.05 (-0.95, 1.06)
Headache days from baseline to post-treatment in the Venlafaxine group *versus* the Placebo group	-1.59 (-2.91, -0.27)	-1.59 (-3.06, -0.12)
DHI-total change in the Venlafaxine group *versus* the Other medicines group (including Placebo group):	-5.16 (-9.30,-1.02)	-5.16 (-9.30,-1.02)
DHI-physical change in the Venlafaxine group *versus* the Other medicines group (including Placebo group):	-1.7 (-3.14, -0.33)	-1.73 (-3.14, -0.33)
DHI-emotional change in the Venlafaxine group *versus* the Other medicines group (including Placebo group):	-2.0 (-3.68, -0.39)	-2.04 (-3.68, -0.39)
DHI-functional change in the Venlafaxine group *versus* the Other medicines group (including Placebo group):	-1.60 (-3.38, 0.19)	-1.60 (-3.38, 0.19)
VSS change between the Venlafaxine group and the Other medicines	-1.1 (-1.86, -0.50)	-1.18 (-1.86, -0.50)
Total efficiency between the Venlafaxine group and Placebo group	18.70 (3.39, 103.09)	18.71 (3.39, 103.14)
Consumption of analgesic change between the Venlafaxine and the Other medications groups	-3.3 (-4.65, -1.99)	-3.3 (-4.65, -1.99)

Table III: Heterogeneity of outcome indicators analysis (venlafaxine *versus* other medicines and placebo).

Factors	Number of references	I^2 (%)	χ^2	p-values
Withdrawals due to AEs in the Venlafaxine group *versus* the Placebo group	3	0	0.06	0.80
Withdrawals due to any reasons in the Venlafaxine group *versus* the Placebo group	3	0	0.2	0.66
Withdrawals due to adverse reactions in the Venlafaxine group *versus* the Other medicines group	6	75	11.81	0.008
Withdrawals due to any reasons in the Venlafaxine group *versus* the Other medicines group	6	79	9.53	0.009
VAS in the Venlafaxine group *versus* the Placebo group	3	33	2.97	0.23
VAS in the Venlafaxine group *versus* the Other medicines group	4	0	1.1	0.58
Migraine duration in the Venlafaxine group *versus* the Other medicines group	4	84	19.25	0.0002
Migraine frequency change in the Venlafaxine *versus* the Other medicines group	4	0.00	0.75	0.69
Headache days from baseline to post-treatment in the Venlafaxine group *versus* the Placebo group	2	19	1.24	0.27
DHI-total change in the Venlafaxine group *versus* the Other medicines group (including Placebo group)	4	0	0.33	0.95
DHI (physical) change in the venlafaxine group *versus* the Other medicines group (including Placebo group):	4	0	0.49	0.49
DHI-emotional change in the Venlafaxine group *versus* the Other medicines group (including Placebo group)	4	0	0.61	0.89
DHI-functional change in the Venlafaxine group *versus* the Other medicines group (including Placebo group):	4	0	0.82	0.84
VSS change between the Venlafaxine group and the Other medicines group	3	0	0.92	0.63
Total efficiency between the Venlafaxine and Placebo groups	2	0	0.01	0.94
Consumption of analgesic change between the Venlafaxine and the Other medications groups	2	0	0.39	0.53

Table IV: The pooled effect of outcome indicators (venlafaxine *versus* placebo /other medicines).

Outcome indicators	SMD/OR	95% CI	Z-values	p-values
Withdrawals due to AEs in the Venlafaxine group *versus* the Placebo group	7.14	0.38,133.60	1.18	0.24
Withdrawals due to any reasons in the Venlafaxine group *versus* the Placebo group	4.33	0.71,26.30	1.59	0.11
Withdrawals due to AEs in the Venlafaxine group *versus* the Other medicines group	0.86	0.08,9.32	0.12	0.9
Withdrawals due to any reasons in the Venlafaxine group *versus* the Other medicines group	0.85	0.24,2.93	0.26	0.79
VAS in the Venlafaxine group *versus* the Placebo group	-0.83	-1.58, -0.09	2.19	0.03
VAS in the Venlafaxine group *versus* the Other medicines group	-0.24	-0.75, 0.26	0.94	0.35
Migraine duration in the Venlafaxine group *versus* the Placebo group	-2.14	-14.04,9.76	0.35	0.72
Migraine duration in the Venlafaxine group *versus* the Other medicines group	-0.06	-1.05, 0.92	0.13	0.90
Migraine frequency change in the Venlafaxine *versus* the Other medicines group	0.05	-0.95, 1.06	0.11	0.92
Headache days from baseline to post-treatment in the Venlafaxine group *versus* the Placebo group	-1.59	-2.91, -0.27	2.36	0.02
DHI-total change in the Venlafaxine group *versus* the Other medicines group (including Placebo group)	-5.16	-9.30, -1.02	2.44	0.01
DHI-physical change in the Venlafaxine group *versus* the Other medicines group (including Placebo group):	-1.73	-3.14, -0.33	2.42	0.02
DHI-emotional change in the Venlafaxine group *versus* the Other medicines group (including Placebo group)	-2.04	-3.68, -0.39	2.43	0.02
DHI-functional change in the Venlafaxine group *versus* the Other medicines group (including Placebo group):	-1.6	-3.38, 0.19	1.75	0.08
VSS between the Venlafaxine and the Other medicines group	-1.18	-1.86, -0.50	3.39	0.0007
Total efficiency between the Venlafaxine and the Other medications group	18.7	3.39, 103.09	3.36	0.0008
Consumption of analgesic change between the Venlafaxine group *versus* the Other medications group	-3.32	-4.65, -1.99	4.91	<0.00001

One study had an unclear risk of bias in selective reporting, and six studies exhibited other sources of unclear bias risk. Detailed information about the risk-of-bias assessment and summary are shown is Figure 2A and 2B. Publication bias was not calculated because the number of included studies was fewer than ten.

For the sensitivity analysis (Table II), the results showed that there was no significant difference between the two models for indicators, including withdrawals due to AEs and any reason, such as migraine duration, migraine frequency change, headache days from baseline to post-treatment, DHI-total change, DHI-physical change, DHI-emotional change, DHI-functional change, VSS, global efficacy, and analgesic consumption change. Therefore, the findings pertaining to these parameters were both consistent and reliable. In contrast, the finding to VAS in the Venlafaxine group *versus* the Placebo group was considered unreliable.

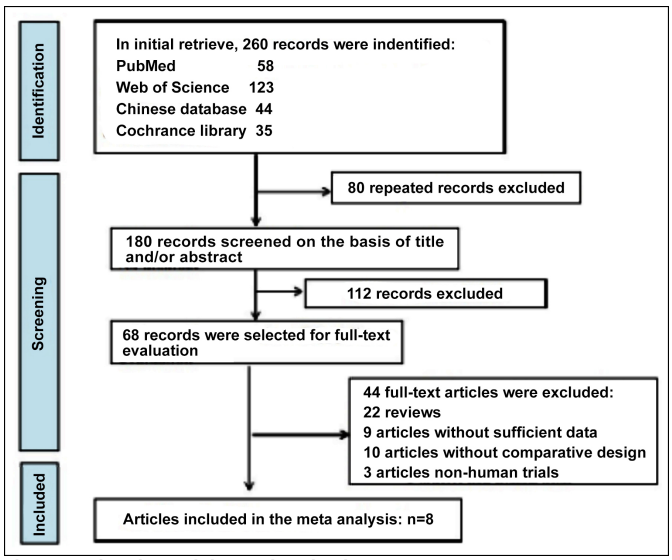

Figure 1: Flowchart of the study selection process.

Figure 2: (A) Risk of bias graph—review authors' judgements about each risk of bias item, presented as percentages across all included studies. (B) Risk of bias summary for the included study.

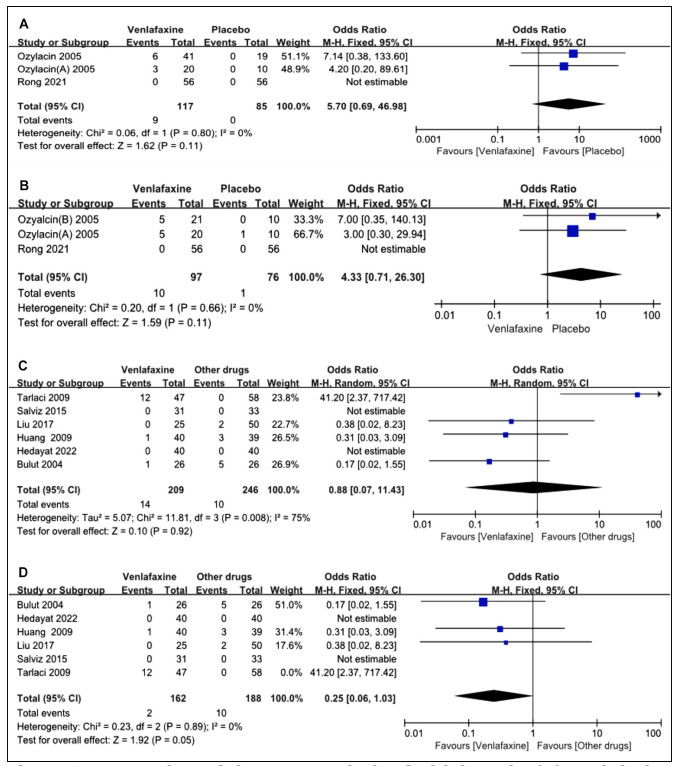

Figure 3: Forest plots of the meta-analysis of withdrawals: (A) Venlafaxine group *versus* Control group; (B) Venlafaxine group *versus* Placebo group; (C) Adverse reactions in the Venlafaxine group *versus* the Other medicines group; and (D) Withdrawals for any reason in the Venlafaxine group *versus* the Other medicines group.

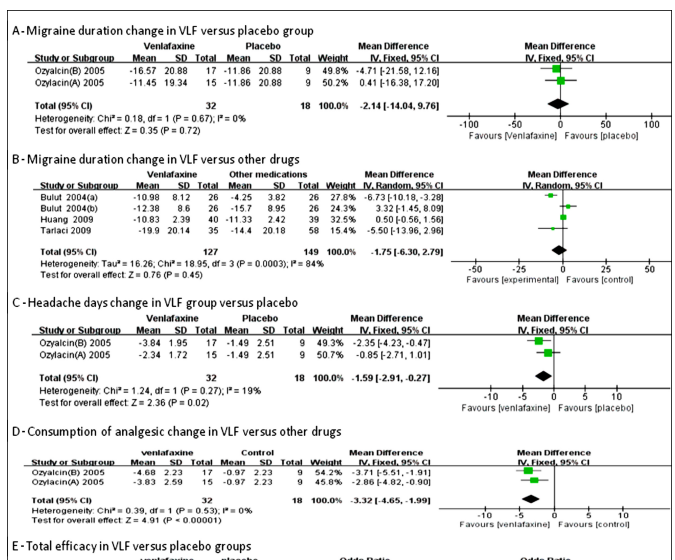

Figure 4: Forest plots of the meta-analysis of migraine indicators: (A) Change in migraine duration in the Venlafaxine group *versus* the Placebo group; (B) Change in migraine duration in the Venlafaxine group *versus* the Other medicines groups; (C) Change in headache days in the Venlafaxine group *versus* the Placebo group; (D) Change in the consumption of analgesic in the Venlafaxine group *versus* the Other medicines group; (E) Total efficacy in the Venlafaxine group *versus* the Placebo group.

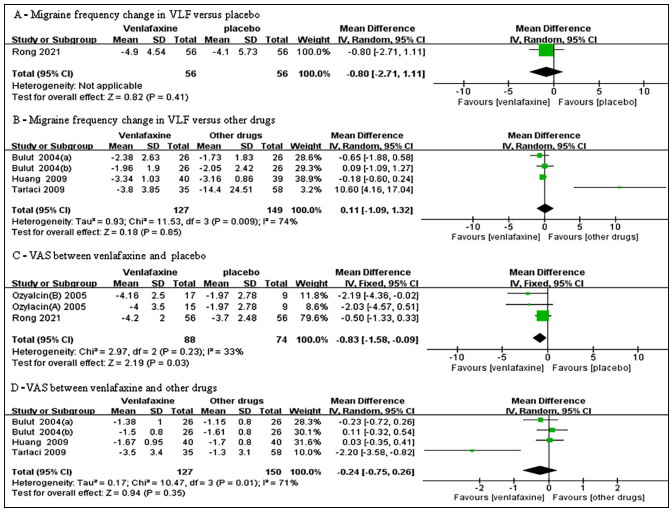

Figure 5: Forest plots of the meta-analysis of showing headache frequency change in the Venlafaxine group *versus* the Placebo group: (A) Migraine frequency change in the Venlafaxine *versus* Placebo groups; (B) Migraine frequency change in the Venlafaxine *versus* the Other medicines group; (C) VAS between the Venlafaxine and Placebo group; (D) VAS between the Venlafaxine group and the Other medicines group.

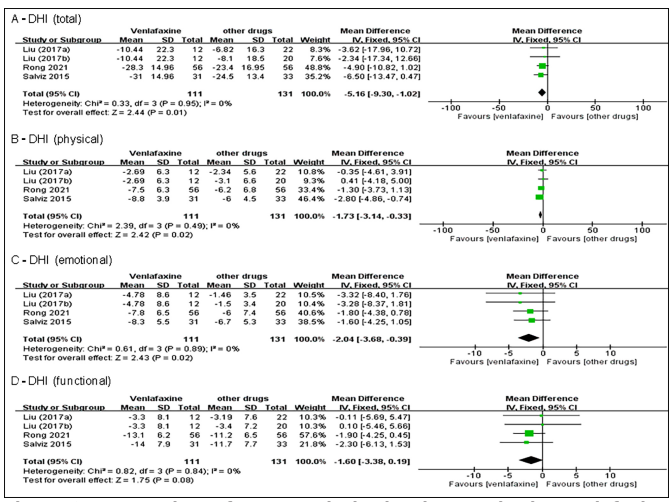

Figure 6: Forest plots of meta-analysis showing DHI in the Venlafaxine *versus* the Placebo groups: (A) DHI-total; (B) DHI-physical; (C) DHI-emotional; (D) DHI-functional.

For the heterogeneity analysis (Table III), the I^2 values for withdrawals due to AEs and any reason, such as migraine duration in the Venlafaxine *versus* the Other medicines group, and VAS in the Venlafaxine *versus* the Placebo group were all greater than 25%, with Chi-square test p-values p <0.01, indicating significant heterogeneity among the studies. Therefore, it was essential to identify the source of heterogeneity by eliminating some individual studies. When the origin of heterogeneity among the studies could not be determined, a random-effects model was utilised to pool the effects. In the case of withdrawals due to AEs in the Venlafaxine *versus* the Other medicines group, the I^2 value was reduced from moderate heterogeneity (73%) to mild heterogeneity after excluding Talaci *et al*.'s article. Therefore, this study was considered as the source of heterogeneity. About withdrawals due to any reason in the Venlafaxine *versus* the Other medicines group, the I^2 value was reduced from 64 to 0% after excluding Talaci *et al*.'s study. About the VAS in the Venlafaxine *versus* Placebo groups, the I^2 value was decreased from mild heterogeneity (33%) to zero heterogeneity (0%) if Rong *et al*.'s study[18] was removed. This article was regarded as the source of heterogeneity. About the change in migraine frequency in the Venlafaxine *versus* the Other medicines group, no study had an impact on the pooled effect. The authors could not identify the heterogeneity source. Therefore, a random-effects model was conducted to pool the effects.

The pooled effects were shown in Table IV. For withdrawals due to AEs or any reason in the Venlafaxine group and the Placebo group, two articles were included.[18,24] The results with zero heterogeneity were obtained (p = 0.80, I^2 = 0). The result showed that the rate of withdrawal due to AEs was not significantly different in the Venlafaxine group than the Placebo group (OR: 5.7; 95% CI 0.69, 46.98; p = 0.11; Figure 3A). Two articles were included to compare the rate of withdrawals for any reason in the Venlafaxine group *versus* the Placebo group.[15,21] It showed that there was no heterogeneity among the studies (p = 0.66, I^2 = 0). The rate of withdrawals because of AEs was not significantly different in the Venlafaxine group *versus* the Placebo group (OR: 4.33; 95% CI 0.71, 26.30; p = 0.11, Figure 3B).

For withdrawals due to AEs in the Venlafaxine group *versus* the Other medicines group, six articles were included.[16,17,19,25-27] The results of moderate heterogeneity were obtained (I^2 = 73%, p = 0.01). Therefore, a random-effect model was used to pool the effects. The result (Figure 3C) showed that the incidence of withdrawal was not significantly different in the Venlafaxine group and the Other medicines group (OR = 0.88; 95% CI 0.07, 11.43; p = 0.92).

For withdrawals due to any reason in the Venlafaxine group *versus* the Other medicines group, the heterogeneity source could not be found. A random effects model was used to pool the effects, which were further analysed. When Talaci *et al*.'s study was deleted, no heterogeneity was found among the studies (I^2 = 0.0%, p = 0.89). Therefore, a fixed-effect model was utilised. The result (Figure 3D) suggested the withdrawal rate for any reason was not significantly different in the Venlafaxine group than the Other medicines group (OR: 0.25; 95% CI 0.06, 1.03; p = 0.05).

For the change in migraine duration, all the four trials reported the changes. Ozylacin *et al*.'s study compared the effects of venlafaxine and placebo[24] and reported no significant difference in the Venlafaxine group as compared to the Placebo group (MD: -2.14; 95% CI -14.04, 9.76; I^2 = 0; p = 0.72). The remaining three studies reported the effects of venlafaxine and other medicines on migraine duration.

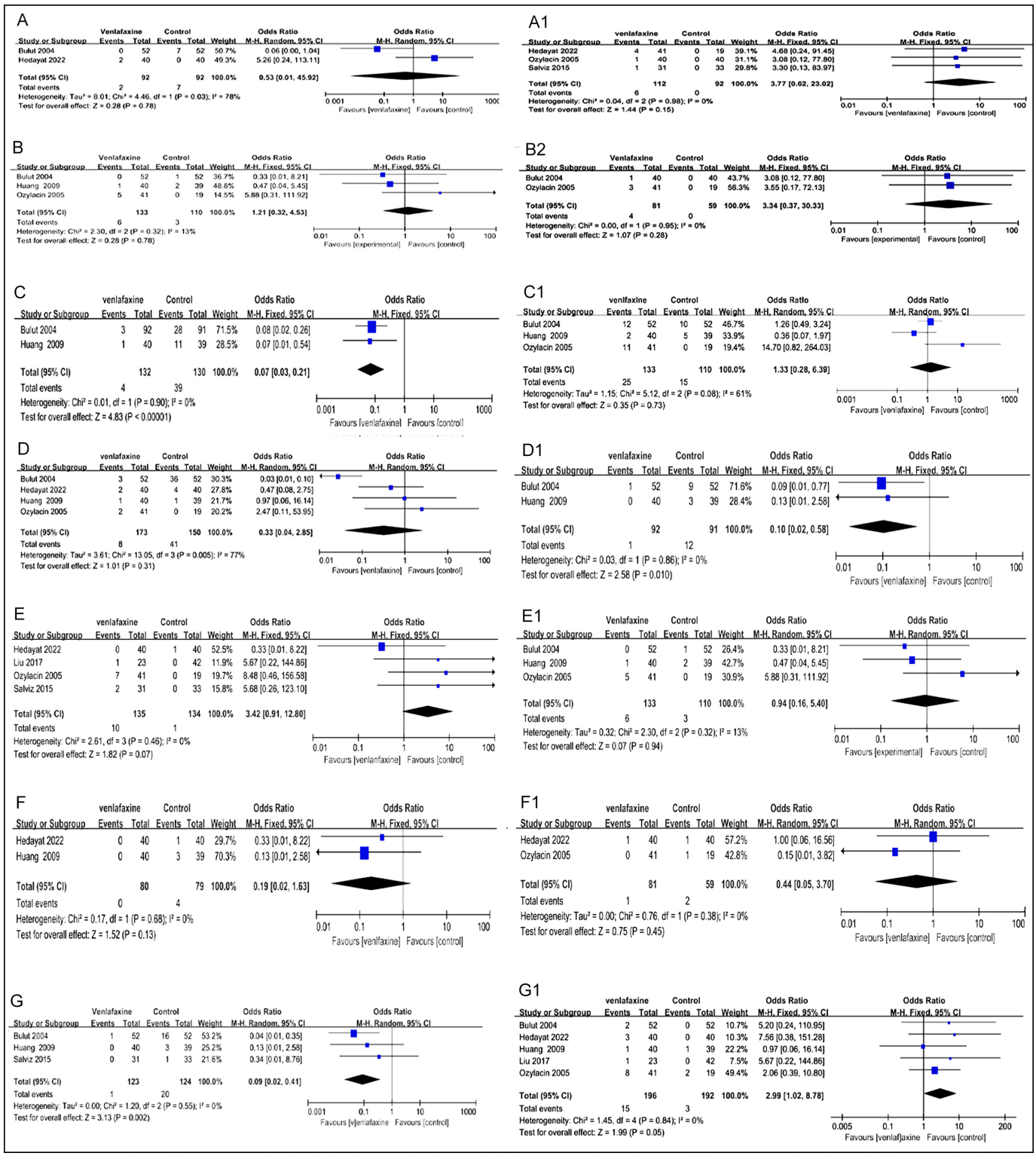

Figure 7: Forest plots of the meta-analysis of showing AEs in the Venlafaxine *versus* the Other medicines groups: (A) Blurred vision rate; (A1) Sexual dysfunction rates; (B) Constipation rate; (B1) Sweating; (C) Difficulty in concentration; (C1) Vomiting; (D) Dry mouth rate; (D1) Forgetfulness; (E) Fatigue; (E1) Nausea rate; (F) Weight again rate; (F1) Increased appetite; (G) Orthostatic hypotension; (G1) Insomnia.

No significant difference was found in the Venlafaxine group as compared to the Other medicines group, including Amitriptyline and Escitalopram groups (MD: -1.75; 95% CI-6.30, 2.79; p = 0.45). Severe heterogeneity was found in the Venlafaxine group and the Other medicines group (I^2 = 84%; p = 0.0003). A random-effects model was used to pool the effect because the heterogeneity source could not be identified (Figure 4A, 4B).

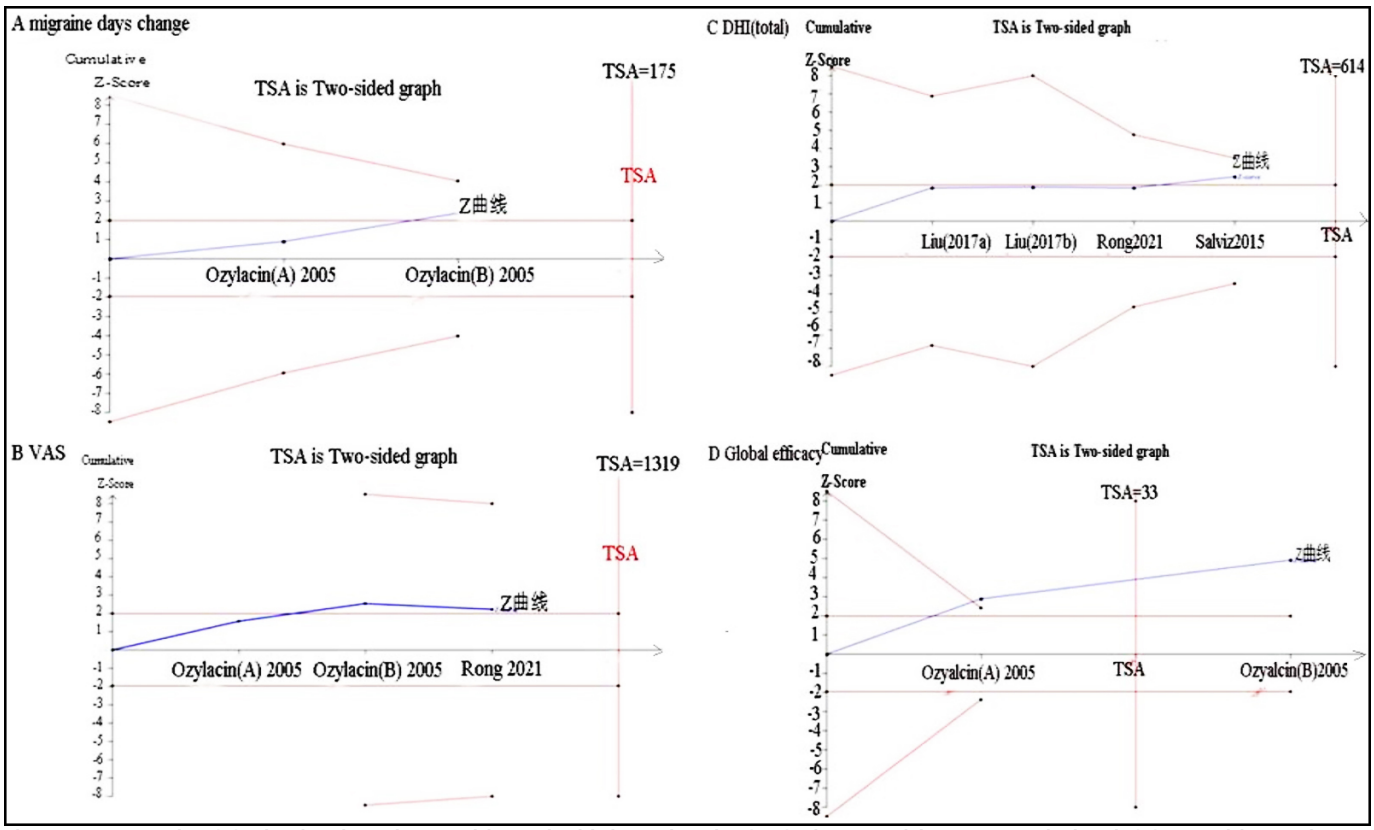

Figure 8: TSA results: (A) Migraine days change with required information size (RIS) of 175 participants was calculated; (B) VAS with RIS of 1,319 participants was calculated; (C) DHI-total, with RIS of 614 participants calculated; and (D) Global efficacy with RIS of 33 participants was calculated.

For migraine days from baseline to post-treatment, one article compared two different doses of medicines.[24] Mild heterogeneity was observed in the result (I^2 = 19%, p = 0.27); therefore, a fixed-effect model was used. Finding (Figure 4C) showed that there was a stronger effect (MD: -1.59, 95% CI -2.91 to -0.27; p = 0.02) in the Venlafaxine group compared to the Other medicine group. Significant difference existed between the Venlafaxine and Placebo groups.

For analgesic consumption, one article (Figure 4D) showed that there was a statistically significant decrease at visit 1 and visit 6 for V75 group and V150 group compared with the Placebo group (MD: -3.32, 95%CI -4.65 to -1.99; p <0.001).[24]

For total efficacy, the result (Figure 4E) showed that there was a statistically significant increase (OR18.70, 95% CI 3.39 to 103.09: I^2 = 0; p = 0.0008) in the Venlafaxine *versus* Placebo groups. Compared to the Placebo group, Venlafaxine group showed a stronger global efficacy without heterogeneity, thereby a fixed-effects model was used.

For the change in migraine frequency from baseline to endpoint, all the six trials were included.[16,17,19,25-27] Venlafaxine exhibited the same reduction effect as compared to other medicines (MD: 0.05; 95% CI -0.95, 1.06; p = 0.92; Figure 5B). Mild heterogeneity with I^2 (65%, p = 0.02) was identified. Therefore, a random-effect model was used. When Talaci *et al*.'s study was deleted, no heterogeneity was found (I^2 = 0; p = 0.69). Then, a fixed-effect model was used. No significant difference was found (MD: -0.15; 95% CI-0.52, 0.22; p = 0.32).

For the VAS (Figure 5C), two studies[18,24] reported this index. It was found that the Venlafaxine group exhibited stronger reduction effect as compared to the Placebo group (MD: -1.13; 95% CI -1.58, -0.09; p = 0.03). Mild heterogeneity (I^2 = 33%, p = 0.23) was found. Therefore, a random-effect model was utilised. Three articles were included to compare the effect of venlafaxine compared to other medicines, including amitriptyline and escitalopram (Figure 5A). Significant heterogeneity existed in the comparative analysis (I^2 =71%; p = 0.01; Figure 5D). Therefore, a fixed-effect model was adopted. Compared to other medicines, there was no significant difference identified in these studies (MD: -0.52; 95% CI -1.37, 0.34; p = 0.24). When Talaci *et al*.'s study was deleted, no significant heterogeneity was found (I^2 = 0; p = 0.77). Hence, a fixed-effect model was utilised. No significant difference was found in venlafaxine as compared to other medicines (MD = -0.01; 95% CI-0.26, 0.24; p = 0.94).

For DHI-total, three studies were included.[18,26,27] A significant improvement in the DHI (physical) was found (MD: -5.16; 95% CI: -9.30, -1.02, p = 0.01), as shown in Figure 6A. Given the low heterogeneity (I^2 = 0%), a fixed-effects model was employed.

A total of 3 studies were included for DHI-physical.[18,26,27] The pooled analysis demonstrated a statistically significant improvement (MD: -1.73; 95% CI: -3.14, -0.33; p = 0.02) under a fixed-effects model (Figure 6B).

Three literatures included for DHI-emotional were pooled for this meta-analysis.[18,26,27] And the result showed a significant reduction in the outcome (MD = -2.04; 95% CI -3.68, -0.39; p = 0.02), as shown in Figure 6C.

For DHI-functional, three studies were included.[18,26,27] The results showed a statistically significant effect (MD:1.60, 95% CI -3.38, 0.19; p = 0.08), as shown in Figure 6D. The calculation of SD in Salviz *et al*.'s research is based on the formula $SD = SE/\sqrt{(1/N_C+1/N_T)}$; the calculation of SD in Liu *et al*.'s study is based on the formula $SD = \sqrt{N}(CL_2+CL_1)/3.92$.

In the analysis of anxiety-related outcomes, one study assessed BAI changes, indicating that both venlafaxine and propranolol significantly reduced BAI scores, albeit without a statistically significant intergroup difference. For vestibular symptom evaluation, two studies involving a three-arm design (venlafaxine, flunarizine, and valproic acid) were incorporated; the pooled results demonstrated a significant improvement with venlafaxine (MD = -1.18; 95% CI -1.86, -0.50; I^2 = 0; p = 0.0007) under a fixed-effect model. Additionally, venlafaxine exhibited superior reductions in HAMA relative to placebo (p = 0.04). Although LWDE outcomes showed numerical improvement in both Venlafaxine and Escitalopram groups, between-group differences were not statistically significant (p = 0.991). Importantly, the observed between-group difference in headache days exceeded the established minimal important difference (MID) of one day, suggesting clinical relevance. Compared to existing reviews, which included only six SNRI studies, the present synthesis underscores venlafaxine's advantage in ameliorating VSS and DHI-emotional, and extends prior evidence by incorporating additional patient-centered endpoints, such as response rate and analgesic use (Figure 7).

About the migraine days from baseline to post-treatment, TSA showed that the Z-curve did not intersect with the TSA boundary value, and the total number of the current combined samples (50) did not reach RIS (175), so there may be a possibility of false positives, suggesting that further studies need at least 125 migraine patients to demonstrate the stability of the results. The result was shown in Figure 8A.

About the VAS, TSA showed that the Z-curve did not intersect with the TSA boundary value, and the sample size has not reached RIS (1319). The total number of the current combined samples is 161. Therefore, there may be a possibility of false positives, suggesting that further studies need at least 1,158 migraine patients to demonstrate the stability of the results. The result was shown in Figure 8B.

About DHI-total, TSA showed that Z-curve did not intersect with the TSA boundary value, and the sample size did not reach the number (RIS = 614). The total number of the current combined samples is 242. It has not reached 614, so there may be a possibility of false positives, suggesting that further studies need at least 372 migraine patients to demonstrate the stability of the results. The result was shown in Figure 8C.

About global efficacy, TSA showed that the Z-curve intersected with the TSA boundary value, and the sample size reached RIS (33). The total number of the current combined samples is 33, which indicated that the result is stable, and no further study was needed to prove this effect. The result was shown in Figure 8D.

DISCUSSION

The analysis on safety and tolerability of venlafaxine showed no obvious difference either in withdrawals rate because of any reason or in the withdrawals rate because of AEs between the Venlafaxine and other active medicines groups, including the Placebo group. This finding is consistent with the outcomes of the previous meta-analysis. To fully understand the effect of venlafaxine on migraine, many outcome indicators mentioned in the study are analysed in this meta-analysis. Although some indicators could not be pooled because of insufficient studies. The authors analysed the effect of venlafaxine on several indicators as follows. Two studies analysed the BDI;[25,26] however, data from Tarlaci *et al*.'s study were not complete and could not be merged, so only descriptive results were presented. Analyses of Salviz *et al*.'s data indicated that venlafaxine reduced BDI score to a higher degree than propranolol, with results showing an MD of -6.60 (95% CI-9.66, -3.54; p <0.001), which was statistically significant. The original study by Salviz *et al*. did not report the SD of the mean difference, which was calculated by RevMan software. The method involved entering the mean and SD values mentioned in the article into RevMan to obtain the mean difference through calculation. Subsequently, the missing SD difference was estimated using the formula $SD = \sqrt{N}(CL_2-CL_1)/3.92$, as mentioned in Yangpeng *et al*.'s meta-analysis.[28]

One study analysed the change in BAI associated with anxiety.[26] Due to limited literature, it was not merged but only described. The results of this study showed that both venlafaxine and propranolol had significant reduction effects on the BAI; however, no significant statistical difference was observed in the effect between the two groups.

Two studies were included because the subjects were randomly assigned to one of the three groups (venlafaxine

group, flunarizine group, and valproic acid group).[26,27] To assess the treatment efficacy on VSS, Liu *et al*.'s study was regarded as two studies, and the results with statistically significant showed an MD of -1.18 (95% CI -1.86 to -0.50; I^2 = 0; p = 0.0007). There was no heterogeneity in the studies. Therefore, a fixed effects model was adopted.

Rong found that venlafaxine had a stronger reduction effect in reducing HAMA compared to placebo (p = 0.05).[18] One article[18] showed that a stronger reduction effect in HAMA (p = 0.04) was observed in venlafaxine compared to placebo.

An analysis of LWDE was not performed due to a lack of relevant studies in the literatures. Tarlaci *et al*. reported that no significant difference existed between patients in the Venlafaxine and Escitalopram groups at baseline.[25]

At the end of the study, both groups showed similar improvements in LWDE (0.78 *vs*. 0.96; p = 0.0001). When the effects of each medicine were examined separately, a greater reduction was observed in the Venlafaxine group. However, when the two medicines were compared directly, no significant difference was found (p = 0.991).

So far, MID has not been established for any headache symptom measures. A one-day between-group difference in headache days was analysed because Silberstein *et al*. demonstrated that a one-day increase in headache days was significantly linked to a reduction in health-related quality of life (HRQOL). The observed difference in headache days exceeded the established MID (1 day), suggesting that it could be considered clinically significant.

Liu *et al*.'s study showed that there were only 6 RCTs, with five articles on venlafaxine[16,24-27] and one on the epinephrine-free dual channel inhibitor, which was duloxetine.[29] Compared to previous reviews that assessed the efficacy of selective serotonin reuptake inhibitors (SSRIs) and SNRIs in the prevention of migraines, where only six SNRI studies were included, venlafaxine treatment had shown significant advantages. Specifically, it outperformed other active agents in reducing VSS and DHI-emotional scores.

Furthermore, the above review did not consider the MID that was important to patients who suffered from migraine headache. Important outcomes including response rate, analgesic consumption, and specific AEs were not analysed in the formed meta-analysis; thereby, analysis was conducted on these indices. Some migraine-related indicators could only be described due to the limited number of available literatures. Meanwhile, as fewer than ten articles were included. Therefore, publication bias could not be analysed using funnel plots or associated quantitative analyses. Therefore, information about publication bias was lacking. Additionally, the data presentation formats in the included literature were not uniform and required conversion to a uniform format before merging and analysis.

CONCLUSION

The current result suggested that venlafaxine may be an effective and safe preventive treatment option for migraine.

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The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
JG, GMX, JHW: Conception and study designed, research process, and manuscript writing.
XBW, YT: Data extraction, data disposal, and quality assessment.
GLW: Manuscript drafting.
JHW: Revision and editing.
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